Management of patients with T2DM and CV disease, Heart Failure or Diabetic Kidney Disease *Does not apply to T1DM

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T2DM + high risk of CVD or established CVD or HF or CKD

Indicators of high risk of CVD:

- End organ damage: proteinuria, LVH, retinopathy, CKD **or**
- 3 or more major risk factors: age ≥55, hypertension, dyslipidaemia, smoking, obesity

Indicators of diabetic kidney disease:

- Reduced eGFR and/or elevated uACR

Multifactorial risk reduction: smoking cessation, diet, exercise, BP control, dyslipidaemia management

1st line treatment

Use **metformin** unless contraindicated or not tolerated

- If HbA1c > target + already on metformin move to 2nd line agent
- If HbA1c ≤ target and already on treatment, consider substituting Gliclazide, Gliptin, Glitazone with SGLT2i or GLP-1 RA and/or reducing insulin doses
- If BMI <27 and HbA1c > 86, discuss with diabetes team since increased risk ketosis

***Metformin/ SGLT2i** should be used in combination **1st line** for CKD/HF*

2nd/ 3rd line treatment + SGLT2-I + GLP-1 RA

CKD predominates	HF predominates	Atherosclerotic CVD predominates
SGLT2 inhibitors (eGFR [ml/min/1.73m2] cut-offs – see product SmPC for up to date info)	**SGLT2 inhibitors** (In HFrEF: Dapagliflozin can be initiated if eGFR ≥15. Empagliflozin eGFR ≥20)	**GLP-1 RA**
Canagliflozin - eGFR ≥60: initially 100mg titrated up to 300mg once daily; eGFR 30-59: 100mg once daily; eGFR <30: do not initiate but continue if uACR >30mg/mmol until dialysis or transplant (CI in these groups) Dapagliflozin – eGFR ≥15: 10mg once daily; eGFR<15: avoid initiation Empagliflozin – eGFR ≥60: initially 10mg titrated up to 25mg once daily; eGFR 30-59: 10mg once daily; eGFR <30: avoid initiation	Canagliflozin, Dapagliflozin or Empagliflozin (Dapagliflozin and Empagliflozin have license in HFrEF)	Choose agent with proven CV benefits (e.g. Semaglutide (SC only) or Liraglutide) • Avoid if history of pancreatitis, gastroparesis or Fx of medullary thyroid cancer • Caution with Semaglutide if more than mild background retinopathy • DPP-4i must be stopped with initiation of GLP-1 RA • hypo risk if adding to SU/ insulin (consider reducing doses)

+/or

Safe prescribing of SGLT2i inhibitors

Check eGFR suitable (see under CKD arm); Avoid if Hx of DKA; Consider reducing loop diuretic dose; hypo risk if adding to SU/ insulin (consider reducing doses)

Patient counselling: Genital Hygiene (5-fold risk genital thrush); Symptoms of DKA; Avoid excess alcohol

"Sick day rules" apply: Withhold if fasting/ dehydrated/ surgery or acutely unwell

+/or

**Diminished glycaemic effect of SGLT-2i with eGFR < 45, however sustained cardio-renal protection*

4th line treatment

Reassess efficacy of treatment change in Diabetes during follow-up

- SU
- Insulin
- DPP-4i if not on GLP1-RA

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; DPP-41 = dipeptidyl peptidase-4 inhibitor; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HbA1c = haemoglobin A1c; HF = heart failure; HFrEF = heart failure reduced ejection fraction; SGLT2i = sodium-glucose co-transporter 2 inhibitor; SU = sulphonylureas; TZD = thiazolidinedione; uACR = urinary albumin creatinine ratio

Type 2 Diabetes – Dose Adjustment in Renal/Hepatic Impairment

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Drug	CKD stages 1&2 eGFR >59 mL/min	CKD stage 3a eGFR 45-59 mL/min	CKD stage 3b eGFR 30-44 mL/min	CKD stage 4 eGFR 15-29 mL/min	CKD stage 5 eGFR <15 ml/min	Mild to moderate hepatic impairment	Severe hepatic impairment
Metformin			Max 500mg twice daily			Specialist initiation only	
Gliclazide		Increased risk hypoglycaemia - Use lowest effective dose					
Alogliptin	25mg	Reduce to 12.5mg daily if eGFR <50		Reduce to 6.25mg daily if eGFR <30			
Linagliptin							
Saxagliptin	5mg	Reduce to 2.5mg daily and avoid in those on dialysis					
Canagliflozin	Initiate 100mg, titrate to 300mg as required	Initiate or continue 100mg only		Continue 100mg if already taking and uACR >30 mg/mmol. Stop if renal replacement therapy. Do not initiate			
Dapagliflozin	10mg				Avoid if eGFR<15		5mg
Empagliflozin (for T2DM)	Initiate 10mg, titrate to 25mg as required	Initiate or continue at 10mg.		Avoid if eGFR<30			
Empagliflozin – HF reduced EF	10mg			Avoid if eGFR<20			
Dulaglutide							
Liraglutide							
Semaglutide							Caution: limited information
Pioglitazone							
Insulin			eGFR<45: Increased risk of hypoglycaemia as kidney main route of insulin clearance				

Type 2 Diabetes – Additional Guidelines

Lifestyle counselling – to be reiterated to patients at every opportunity

Dietary guidance – seek dietician input. Individualised approach: low fat diet, low Glycaemic index diet or Mediterranean diet etc. If obese with type 2 diabetes duration <6 years, consider patient for counterweight plus (very low calorie diet with aim of significant weight loss and possibility of reversing diabetes).

Physical activity – Realistic targets should be set. Clinical studies show that walking 30mins every day has CV benefits.

Weight management – Realistic initial weight loss target of 5-10% of starting weight.
Consider drug therapy e.g. SGLT2-I and GLP-1RAs.

Smoking cessation and alcohol consumption – Refer smoking cessation team. Alcohol may influence glucose control (both Hypo/ Hyper glycaemia).

Sick Day Guidance - to be reiterated to patients at every opportunity
When unwell (acute illness: fevers, sweats, rigors, vomiting, diarrhoea, fasting etc.) Omit:

S – SGLT2-i
A – ACEi/ ARNI (Entresto)
D – Diuretics
M – Metformin
A – ARBs
N – NSAIDs

Type 2 Diabetes – Additional Guidelines

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General safety advice for prescription of SGLT2i

A small drop in eGFR (<30%) may occur within first 4-6 weeks of commencement. This should stabilise and is similar to that seen with ACE inhibitors. There is no evidence that eGFR measurement at an interval after initiation can identify patients who are intolerant and we do not recommend routine blood checks specifically to assess effect on GFR at this time point. SGLT2i are potassium neutral.

The risk of diabetic ketoacidosis (DKA) is elevated (with SGLT2i), including euglycaemic DKA. There is a mechanistic association with glycosuria and ketogenesis and this can be exacerbated during periods of physiological stress. The risk of this complication is small, particularly if good sick day guidance is provided.

There should be caution where:

- People who have rapidly progressed to requiring insulin (within one year of diagnosis)
- Past history of DKA
- History of pancreatic disease – including alcoholic pancreatitis as a cause of their diabetes

Research Evidence

Given the recent wealth of publications regarding cardiovascular & renal outcome trials in type 2 diabetes, this Type 2 Diabetes Management Algorithm is meant as a quick reference guide as we move away from glucose-centric prescribing, based on current evidence as of February 2021. For more in-depth guidance please refer to the EASD-ADA consensus document or other (inter)national guidelines.

In summary, the glucose-centric view of vascular complications works in relation to retinopathy, but is insufficient on its own with respect to the prevention and management of macrovascular disease in diabetes. It is time for action to ensure that patients with diabetes at high cardiorenal risk receive the benefits of GLP-1 receptor agonists and SGLT2 inhibitors through the collaboration of practitioners involved in their care.

Table 1. Cardiovascular outcome trials with SGLT2 inhibitors in type 2 diabetes (adapted from Marx et al. Lancet Diabetes Endocrinol 2020)

	EMPA-REG Outcome (Empalgiflozin) [1]	CANVAS Programme (Canagliflozin) [2]	CREDENCE (Canagliflozin) [3]	DECLARE-TIMI 59 (Dapagliflozin) [4]
Three-point MACE*	0·86 (0·74–0·99; p=0·04)	0·86 (0·75–0·97; p=0·02)	0·80 (0·67–0·95; p=0·01)	0·93 (0·84–1·03; p=0·17)
Heart failure admission	0·65 (0·50–0·85; p=0·002†)	0·67 (0·52–0·87)	0·61 (0·47–0·80; p<0·001)	0·73 (0·61–0·88)
CV death	0·62 (0·49–0·77; p<0·001†)	0·87 (0·72–1·06)	0·78 (0·61–1·00; p=0·05)	0·98 (0·82–1·17)

*Data are hazard ratio (95% CI; p value [if available]). MACE=major adverse cardiovascular events. *Three-point MACE consists of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. †Nominal p value*

Table 2. Cardiovascular outcome trials with GLP-1 receptor agonists in type 2 diabetes (adapted from Marx et al. Lancet Diabetes Endocrinol 2020)

	LEADER (Liraglutide) [5]	SUSTAIN 6 (subcutaneous Semaglutide) [6]	REWIND (dulaglutide) [7]
Three-point MACE*	0·87 (0·78–0·97; p=0·01)	0·74 (0·58–0·95; p=0·02	0·88 (0·79–0·99; p=0·026)
Stroke	0·89† (0·72–1·11; p=0·3‡)	0·61† (0·38–0·99; p=0·04‡)	0·76† (0·61–0·95; p=0·017‡)
Myocardial Infarction	0·88§ (0·75–1·03; p=0·11‡)	0·74§ (0·51–1·08; p=0·12‡)	0·96§ (0·79–1·16; p=0·65‡)
CV death	0·78 (0·66–0·93; p=0·007‡)	0·98 (0·65–1·48; p=0·92‡)	0·91 (0·78–1·06; p=0·21‡)

*Data are hazard ratio (95% CI; p value [if available]). MACE=major adverse cardiovascular events. *Three-point major adverse cardiovascular events consists of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. †Non-fatal stroke only. ‡Nominal p value. §Non-fatal myocardial infarction only.*

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David Carrick, Sandeep Thekkepat, March 2022, review date March 2023